

*REMARKS/ARGUMENTS.*

*The Pending Claims*

Claims 41-56 are new and are directed to screening methods for candidates of a substance having (i) feeding suppressive activity or blood sugar level suppressive activity (claims 41, 42, and 45-50) or (ii) feeding promoting activity (claims 43, 44, and 51-56).

*Amendments to the Claims*

The non-elected claims in response to the restriction requirement have been canceled. In addition elected claims 18-21, 31-35, and 38 have been canceled and rewritten as new claims 41-56. As such, new claims 41-56 pertain to similar subject matter as elected (and now canceled) claims 18-21, 31-35, and 38. The new claims are supported by the originally filed claims and the specification at, for example, page 32, lines 17-32; page 33, line 15, through page 35, line 14; and page 36, line 28, through page 37, line 13. No new matter has been added by way of these amendments.

*Summary of the Office Action*

The Office Action makes final the restriction requirement and withdraws non-elected claims 1-17, 22-30, 36, 37, 39, and 40 from consideration.

The Office Action objects to claims 18-21, 31-35, and 38 for encompassing non-elected subject matter in response to the restriction requirement.

The Office Action rejects claims 18-21, 31-35, and 38 under (a) 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement and written description, (b) 35 U.S.C. § 112, second paragraph, as allegedly indefinite, (c) 35 U.S.C. § 101, and (d) 35 U.S.C. § 103(a) as allegedly obvious in view of Burmer et al. (U.S. Patent Application Publication 2003/0113798 A1), Wilson et al. (*Br. J. Pharmacol.*, 125: 1387-1392 (1998)), and Milligan et al. (*Trends Pharmacol. Sci.*, 20: 118-124 (1999)).

Reconsideration of the objection and the rejections is hereby requested.

*Discussion of Claim Objection*

The Office Action objects to claims 18-21, 31-35, and 38 for encompassing non-elected SEQ ID NO: 4 and for depending from non-elected claims 13, 16, 24, and 27. Claims 18-21, 31-35, and 38 have been canceled. New claims 41-56, which are similarly directed to screening methods, do not recite SEQ ID NO: 4. Accordingly, the claim objection has been rendered moot and should be withdrawn.

*Discussion of the Section 112, First Paragraph, Rejections*

The Office Action rejects claims 18-21, 31-35, and 38 for allegedly lacking enablement and written description. As discussed above, these claims have been canceled. While new claims 41-56 are directed to similar screening methods, the new claims recite that the screening system comprises a lipid bilayer membrane comprising (a) a polypeptide consisting of an amino acid sequence of SEQ ID NO: 2 or an ortholog thereof and (b) a G protein  $\alpha$  subunit belonging to the Gs family (or a G protein  $\alpha$  subunit belonging to the Gi or Gq family, wherein about 5 amino acids of the G protein  $\alpha$  subunit is replaced with that of a G protein  $\alpha$  subunit belonging to the Gs family), wherein the C-terminus of the polypeptide optionally can be ligated to the N-terminus of the G protein  $\alpha$  subunit.

The Office Action contends that the specification fails to establish that GPRC5D is a therapeutic target for cibophobia or lifestyle-related diseases, such as diabetes, obesity, hyperlipidemia, and hyperuremia. The specification, however, teaches that the inventive screening system can be used for identifying therapeutic substances to treat the underlying causes of these diseases (e.g., by affecting feeding suppressive activity, blood sugar level suppressive activity, and/or feeding promoting activity).

The hypothalamus is an organ that expresses feeding regulatory factors, such as ghrelin, leptin, and the like, as well as receptors thereof. The hypothalamus affects systemic sugar metabolism via insulin receptors and glucose-responsive neurons. The expression of GPRC5D in the hypothalamus strongly suggests that this receptor is a feeding/blood sugar regulatory factor (see Reference Examples 1 and 2 at specification pages 52-53).

Antisense DNA generally is known to suppress the expression of its target protein, resulting in suppression of the function of the target protein. Antisense technology is an

established methodology for elucidating the function of a protein of interest. Antisense-mediated knockdown clearly confirms the function of a target protein. In the case of GPRC5D, antisense administration causes a reduction in the amount of the receptor on cell surfaces, which results in reduced intracellular signal transmission via the receptor.

As set forth in Example 1 of the specification, food consumption increased when antisense DNA against GPRC5D was administered into the cerebral ventricles of mice (as compared with the administration of a control DNA). The results clearly demonstrate that a substance inhibiting the expression and function of GPRC5D induces increased food consumption in an animal, such as in a mouse model. In the therapy of cibophobia, it is necessary to increase food consumption to improve extreme malnutrition. Therefore, the specification clearly demonstrates the therapeutic activity of a GPRC5D antagonist for cibophobia.

Furthermore, Nakazato et al. (*Nature*, 109: 194-197 (2001), a copy of which is submitted herewith) discloses that ghrelin, which is the ligand for a receptor expressed in the hypothalamus, increases food consumption in a rat via its receptor (see Abstract; page 195, first column, lines 6-10; and Figure 1a). Nakazato et al. concludes that ghrelin is a physiological mediator of feeding (see paragraph bridging pages 194-195). Akamizu et al. (*European Journal of Endocrinology*, 150: 447-455 (2004), a copy of which is submitted herewith) reports that the administration of ghrelin resulted in an increased hunger sensation in humans in a Phase I trial (Phase II trial is underway; see Abstract and page 451, first column, lines 3-13). These findings support the teaching in the specification that a substance (e.g., a GPRC5D antagonist) showing feeding stimulating activity in an animal model is a candidate for an appetite stimulator in humans.

Additionally, as set forth in Example 1 of the specification, blood sugar levels in mice significantly increased following administration of an antisense DNA against GPRC5D. These results clearly demonstrate that the suppression of GPRC5D function exacerbates diabetic symptoms. Therefore, one of ordinary skill in the art would reasonably expect that a substance enhancing the expression and function of GPRC5D improves diabetic symptoms in individuals via decreased blood sugar levels.

Given the teachings in the specification and what was known in the art at the time of the filing of the application, one of ordinary skill in the art would recognize that that specification clearly describes the inventive subject matter and how to make and use the screening methods of the invention to identify candidate therapeutic substances.

Accordingly, the rejections for lack of enablement and written description should be withdrawn.

*Discussion of the Section 112, Second Paragraph, Rejection*

The Office Action contends that the terms “therapeutic activity,” “lifestyle-related disease,” “activity of the effector,” and “activity” are unclear and, therefore, that the scope of the claims that recite these terms is unclear. As discussed above, claims 18-21, 31-35, and 38 have been canceled. New claims 41-56 do not recite these terms. The indefiniteness rejection, therefore, has been rendered moot and should be withdrawn.

*Discussion of the Provisional Section 101 Rejection*

The Office Action provisionally rejects claims 18-21, 31-35, and 38 under 35 U.S.C. § 101 for allegedly claiming the same invention as that of claims 18-21, 31-33, and 35 of copending U.S. Patent Application 10/491,654 (“the ‘654 application”). As discussed above, claims 18-21, 31-35, and 38 have been canceled. Should the Office consider that the provisional rejection over the ‘654 application applies to new claims 41-56, Applicants will address the rejection upon notice that the ‘654 application will issue as a patent with the cited claims.

*Discussion of the Section 103(a) Rejections*

As discussed above, claims 18-21, 31-35, and 38 have been canceled. New claims 41-56 are directed to screening methods for substances that can be used to treat particular diseases (e.g., cibophobia, diabetes, obesity, hyperlipidemia, and hyperuremia). In particular, new claims 41-56 are directed to screening for candidates of a substance having (i) a feeding suppressive activity or blood sugar level suppressive activity or (ii) feeding promoting activity.

The Burmer, Wilson, and Milligan references do not teach or suggest that GPRC5D can be a target for a therapeutic agent for cibophobia or other lifestyle-related diseases.

Therefore, one of ordinary skill in the art would not be motivated to combine the disclosures of the Burmer, Wilson, and Milligan references in such a way as to arrive at the present invention. Indeed, even if one of ordinary skill in the art were motivated to combine the disclosures of the Burmer, Wilson, and Milligan references, one would not arrive at the inventive subject matter, since the cited references do not teach or suggest screening for candidates of a substance having (i) a feeding suppressive activity or blood sugar level suppressive activity or (ii) feeding promoting activity, through use of a screening system based on GPRC5D. Under the circumstances, the obviousness rejection should be withdrawn.

*Conclusion*

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



John Kilyk, Jr., Reg. No. 30,63  
LEYDIG, VOIT & MAYER, LTD.  
Two Prudential Plaza, Suite 4900  
180 North Stetson Avenue  
Chicago, Illinois 60601-6731  
(312) 616-5600 (telephone)  
(312) 616-5700 (facsimile)

Date: January 25, 2007